Sponsor: Sanofi **Drug substance(s):** rilzabrutinib	**Study Identifiers:** NCT04748926, U1111-1260-4526 **Study code:** PRN1008-024/INT17090

Title of the study:

An Open-Label, Phase I, Two-Part Drug-Drug Interaction Study to Evaluate the Effects of Quinidine and Rifampin on the Single-Dose Pharmacokinetics and Safety of Rilzabrutinib (PRN1008) in Healthy Male and Female Volunteers

Study center(s):

This study was conducted at 1 center in United States

Study period:

Study initiation date: 18 Dec 2020 (signed informed consent)

Study completion date: 15 Feb 2021 (last participant last visit)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary

- To evaluate the impact of quinidine co-administration on rilzabrutinib pharmacokinetics (Part A).
- To evaluate the impact of rifampin co-administration on rilzabrutinib pharmacokinetics (Part B).

Secondary

- To assess the safety and tolerability of single oral doses of rilzabrutinib administered alone and with quinidine or rifampin.
- To characterize the PK of quinidine in the presence and absence of rilzabrutinib (Part A)

Methodology:

This was a single center, two-part study to evaluate the effect of the strong CYP3A enzyme inducer rifampin and the P-glycoprotein (P-gp) efflux pump inhibitor quinidine on the pharmacokinetics (PK) and safety of rilzabrutinib.

Part A of the study evaluated the effect of quinidine on rilzabrutinib PK, and Part B evaluated the effect of rifampin on rilzabrutinib PK. Each Part was an open-label, fixed-sequence, 2 period, 2 intervention study in healthy volunteers.

An eligibility Screening period took place between Days -28 and -1. All subjects found eligible and enrolled in the study were confined at the clinical site from Day -1 until the Period 2 last assessments were completed. Eligibility to enroll was established prior to dosing on Day 1. All subjects (per Part) completed both periods of the study.

Rilzabrutinib with and without the concomitant drug was administered after a 10 hour overnight fast. Study periods were separated by a washout of 4 days.

All doses of quinidine from Day 7 to 9 and Day 11, and rifampin from Day 7 to 15 and Day 17 were administered either 1 hour before or 2 hours after a meal, except for days on which rilzabrutinib was administered. Subjects who participated in Part A could not participate in Part B.

Number of study participants:

Planned: Part A – 16 subjects, Part B – 16 subjects

Randomized: Part A – 16 subjects, Part B – 16 subjects

Treated: Part A – 16 subjects, Part B – 16 subjects

Evaluated:

Efficacy/pharmacodynamics: NA

Safety/PK: Part A - The Safety analysis and PK analysis sets consisted of 16, 16, and 9 subjects in Period 1, Period 2 quinidine, and Period 2 co-administration phase, respectively. Part B - The Safety analysis sets consisted of 16, 16, and 16 subjects and the PK analysis sets of 16, 0, and 16 subjects in Period 1, Period 2 rifampin, and Period 2 coadministration phases, respectively.

Diagnosis and criteria for inclusion:

1) Non-smoking, non-vaping, and non-tobacco using, healthy males and non-pregnant, non-lactating females 18 to 65 years of age (inclusive) at the time of signing the informed consent.

2) Body mass index (BMI) within the range of 18.0 to 35.0 kg/m^2 (inclusive)

Study products

Investigational medicinal product: 400 mg rilzabrutinib

Formulation: Tablet

Route of administration: oral

Dose regimen: single dose, 400 mg

Noninvestigational medicinal product(s): Part A - Quinidine. Part B - Rifampin

Formulation: Part A - tablet. Part B - capsule

Route of administration: Part A - oral. Part B - oral

Dose regimen: Part A – 300 mg Q8h for 5 days. Part B – 600 mg QD for 11 days

Duration of study intervention: As described above

Duration of observation: The duration of the study was approximately 50 days, including the Screening period

Criteria for evaluation:

Efficacy/pharmacodynamics: NA

Safety: Adverse events reported by the subject or noted by the Investigator. Standard hematology and blood chemistry.

Pharmacokinetics:

Part A - Rilzabrutinib plasma pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, CL/F, V_z/F, and $t_{1/2}$) with and without the concomitant drug (quinidine). Geometric mean ratios and 90% confidence intervals were calculated for C_{max}, $AUC_{0\text{-}last}$, and AUC0-inf (Part A).

Part B - Rilzabrutinib plasma pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, CL/F, V/F, and $t_{1/2}$) with and without the concomitant drug (rifampin). Geometric mean ratios and 90% confidence intervals were calculated for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ (Part B).

Statistical methods:

PK parameters were calculated from plasma rilzabrutinib concentrations using standard noncompartmental methods and include C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, CL/F, V/F and half-life. Other PK parameters were generated as appropriate. Plasma concentrations and computed PK parameters were listed and summarized descriptively by part intervention and timepoint. Individual and mean plasma concentration versus time data were presented graphically.

Two separate statistical analysis were performed for rilzabrutinib; In Part A, to assess the effect of co-administration of quinidine on rilzabrutinib in plasma, the estimated means difference (quinidine and rilzabrutinib [Test] – rilzabrutinib alone [Reference]) and its 90% confidence interval limits (CI) on the log-scale was constructed. In Part B, to assess the effect of co-administration of rifampin on rilzabrutinib in plasma, the estimated means difference (rifampin and rilzabrutinib [Test] – rilzabrutinib alone [Reference]) and its 90% CI on the log-scale was constructed.

For each primary PK parameter ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}), an estimate of the adjusted geometric mean ratios (GMR) for the comparison of interest (Test/Reference) was calculated by exponentiation of the difference between estimated least squares means. Similarly, the 90% CI of the estimated means difference was back-transformed to obtain the results on the original scale (ie, to calculate the 90% CI of the GMR).

Summary Results:

Population characteristics: Part A - A total of 16 healthy subjects were enrolled in Part A of the study. Of these, 8 subjects completed the study and 8 subjects discontinued early because of AEs (prolonged QTc). The majority of participants were women (56.3%), White (87.5%) and were of Hispanic or Latino ethnicity (81.3%). The mean age was 46.3 years and ranged from 21 to 64 years. The mean BMI was 26.87 kg/m^2.

Part B - A total of 16 healthy subjects were enrolled in Part B of the study. All 16 subjects completed the study. The majority of participants were women (81.3%), White (93.8%) and were of Hispanic or Latino ethnicity (100.0%). The mean age was 51.4 years and ranged from 27 to 65 years. The mean BMI was 29.13 kg/m^2.

Safety results: Part A - Overall, 11 of 16 subjects (68.8%) reported a total of 20 TEAEs. The most frequently reported AEs were in the SOC categories of Investigations, Gastrointestinal Disorders, and Cardiac Disorders and included TEAEs of electrocardiogram QT prolonged (8 of 16 subjects; 50.0%), diarrhea (4 of 16 subjects; 25.0%), and palpitations (4 of 16 subjects; 25.0%). All TEAEs were reported as mild/grade 1, resolved, and non-serious. A total of 8 subjects reported a TEAE leading to discontinuation of the study (ECG findings of QTc prolongation) of which 7 subjects were discontinued during the quinidine only phase and one was discontinued during the coadministration phase. All TEAEs of electrocardiogram QT prolonged were reported as mild/grade 1, non-serious, and resolved without sequalae; all were considered related to quinidine use (none were reported as being related to rilzabrutinib).

Part B **-** Overall, 9 of 16 subjects (56.3%) reported a total of 11 TEAEs. The most frequently reported AEs were in the SOC categories of Renal/Urinary Disorders and Gastrointestinal Disorders and included TEAEs of chromaturia (6 of 16 subjects; 37.5%) and diarrhea (3 of 16 subjects; 18.8%). All TEAEs were reported as mild/grade 1, resolved, and non-serious. No TEAEs were reported that led to study drug discontinuation (drug withdrawn) or to discontinuation of the study. No deaths or serious adverse events (SAEs) were reported.

Pharmacokinetic results:

Part A: Summary of Plasma Rilzabrutinib Relative Bioavailability (PK Analysis Set)

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Parameter	n	Geometric LSMean[a]	Ratio [(Rilzabrutinib + Quinidine)/ Rilzabrutinib Only]	
			Geometric LSMean Ratio[a]	90% CI[a]
C_{max} (ng/mL)				
Rilzabrutinib + Quinidine	9	92.2949	0.864	0.647, 1.154
Rilzabrutinib Only	9	106.7823		
$AUC_{0\text{-}last}$ (hr*ng/mL)				
Rilzabrutinib + Quinidine	9	384.5	1.069	0.803, 1.423
Rilzabrutinib Only	9	359.7		
$AUC_{0\text{-}\infty}$ (hr*ng/mL)				
Rilzabrutinib + Quinidine	6	340.6	1.127	0.919, 1.382
Rilzabrutinib Only	6	302.3		

a: From an ANOVA model for the log transformed parameter results with fixed effect treatment and random effect subject.
Source: CSR Section 15.4, Table 14.2.5.1

Part B: Summary of Plasma Rilzabrutinib Relative Bioavailability (PK Analysis Set)

Parameter	n	Geometric LSMean[a]	Ratio [(Rilzabrutinib + Rifampin)/ Rilzabrutinib Only]	
			Geometric LSMean Ratio[a]	90% CI[a]
C_{max} (ng/mL)				
Rilzabrutinib + Rifampin	16	25.8616	0.195	0.165, 0.231
Rilzabrutinib Only	16	132.4346		
$AUC_{0\text{-}last}$ (hr*ng/mL)				
Rilzabrutinib + Rifampin	16	86.63	0.199	0.166, 0.239
Rilzabrutinib Only	16	434.6		
$AUC_{0\text{-}\infty}$ (hr*ng/mL)				
Rilzabrutinib + Rifampin	14	101.6	0.205	0.167, 0.251
Rilzabrutinib Only	14	496.7		

a: From an ANOVA model for the log transformed parameter results with fixed effect treatment and random effect subject.
Source: CSR Section 15.4, Table 14.2.5.2

Issue date: 01-Dec-2025